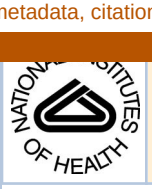

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Relationship between hyperglycemia and the risk of tuberculosis in Asian HIV positive individuals in the antiretroviral therapy era: cohort study

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Keywords

Tuberculosis; HIV; AIDS; Diabetes mellitus; glucose; hyperglycaemia

INTRODUCTION

Many low-middle income countries, including in Asia, are now facing the intersection of two epidemics-of communicable and non-communicable diseases, including diabetes mellitus (DM) and tuberculosis (TB) specifically.[1] DM has been recognised as an important risk factor for TB in the general population, especially in the TB endemic settings.[1,2] Poorly controlled diabetics (with HbA1C>7%) are the main group at a higher risk of TB.[1] Finally, DM is also believed to elevate the risk of serious infections in general.[3] Although the mechanisms of these associations are not clear, they are thought to be directly related to hyperglycemia and cellular insulinopenia, as well as indirect effects of hyperglycemia on macrophage and lymphocyte function.[1,3]

HIV-positive individuals are at high risk of TB.[4] Further, diabetes has emerged as one of the important co-morbidities in HIV-positive individuals, especially in the antiretroviral therapy

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(ART) era.[5,6] However, the relationship between blood glucose levels and TB in HIV positive population has been remarkably understudied.[7,8] Investigating this relationship in HIV-positive individuals is important not only for better clinical management of HIV but also for TB control in general. In this study, we model the relationship between fasting blood glucose and risk of TB in the TREAT Asia HIV Observational Database (TAHOD), a multi-country Asian cohort of HIV-positive individuals.

METHODS

Study population

TAHOD is a clinical cohort study of patients with HIV infection in Asia which began in 2003. The detailed methodology has been published elsewhere.[9] Data are collected from 21 clinical sites in 12 countries and territories in Asia and transferred electronically to the Kirby Institute every March and September. Ethical approval was obtained from the University of New South Wales, Sydney, Australia, and all sites institutional review boards. For this analysis, we included patients from TAHOD who had at least one glucose measurement, at least 6 months of further follow-up, and no known TB at or before study entry.

Measurement of blood glucose

In TAHOD, blood glucose tests and results only started to be reported from a median year of 2008 (interquartile range (IQR): 2005-2010). Blood glucose values are measured according to the local sites' standard of care, and when measured, are captured during routine data transfer. All values are expected to be measured after 8-12 hr fasting.

Outcome

The primary outcome was any diagnosis of TB, including both definitive and presumptive diagnoses. The diagnostic criteria and the validation procedure used in TAHOD have been published elsewhere.[9, 10]

Statistical analyses

We used Cox proportional hazard regression to model the relationship between glucose and the outcome.[11] Time at risk began at the first glucose measurement and ended at the occurrence of the first event or lost to follow-up/death or censorship date of 31-March-2013.The main exposure factors were baseline (at study entry) and time-updated (latest) blood glucose which were categorised as deciles to assess for any non-linear relationship with the incidence-rate of the outcome. We also analysed glucose as diabetic range (≥7mmol/L as per American Diabetes association guidelines[12]) ever recorded in the follow-up as the fixed variable. Models were adjusted for key risk factors[10], which included gender, reported injecting drug use (IDU) as mode of transmission, and age at study entry. Time-updated covariates included CD4 count (categorised as <200, 200-350 and >350 cells/mm^3), body mass index (BMI) defined as weight (kg)/height(m^2) and categorised as <18.5, 18.5-25, 25-30, >30 or missing, and receipt of ART. Once started, receipt of ART was analysed as intention-to-treat. HIV viral load was not used in models due to concerns about the missing data and collinearity. All time-updated variables were carried forward when missing. Models were further stratified by clinical site, which also accounted for

varying TB endemicity across the region. Recording of isoniazid primary prophylaxis is not complete in TAHOD. Sensitivity analysis was conducted by either adjusting for or excluding those who received isoniazid prophylaxis where known.

RESULTS

Of the potentially 8488 eligible patients, 4617 (19000 person-years of the follow-up) were eligible for inclusion in the analysis. At cohort entry, those included (vs. excluded) were more likely to be female, older, not reporting IDU and from a low TB burden country site as defined by WHO.[10, 13]

At study entry, the mean age (standard deviation) was 38 (9.9) years, 67% were male, 5.4% reported IDU, and 63% were from a high TB burden country. The median CD4 count was 269 (IQR: 140-430) cells/mm^3, BMI was 21.4 (IQR: 19.3-23.7) kg/m^2 (missing in 32%) and glucose was 5 (IQR: 4.6-5.5) mmol/L. A vast majority (95.7%) started ART at some point in the follow-up. Patients had a median (IQR) of 4 (2-8) glucose measurements, and the median interval between glucose measurements was 5 (3-8) months.

There were 303 TB events at a rate of 1.58/100 person-years (95% confidence interval: 1.41-1.76). There was a U or inverse J-shaped relationship between the glucose (baseline or latest) and the outcome, with the highest risk at both the extremes and the lowest risk at the middle categories (Table-1). The risk was about 2-fold in the tenth decile (fasting blood glucose of >6.5mmol/L) compared to the sixth decile (reference category). Baseline glucose was a significant factor in both, unadjusted and adjusted models, stratified by site (Table-1). Latest glucose also showed a similar trend and was a significant factor in unstratified models (not shown), although the P-value for latest glucose became non-significant after stratifying by site due possibly to loss of power[11, 14]. Further, occurrence of diabetic range of glucose ever in the follow-up was also associated with the higher risk of TB in all models (Table-1). Results were not sensitive to further adjustment or exclusion of those who were known to have received INH prophylaxis (7.5% of participants) (not shown).

DISCUSSION

We found that higher levels of glucose are associated with the greater risk of TB. The effect persisted even after analysing baseline or latest glucose levels, thereby minimising the possibility of reverse causality (i.e. TB affecting the glucose) and suggest that high glucose is likely to be associated with the prospective risk of TB.

Only a few other studies have assessed this relationship in HIV-positive individuals. Two studies from India and Tanzania, respectively, found diabetes to be an important co-morbidity in HIV-TB co-infected patients, although the HIV-positive individuals in these studies were with lower CD4 count and not on ART.[15, 16]

Unexpectedly, we also found risk to be higher at the extreme low end of the measured glucose. People with low glucose were also more likely to be with low BMI. The later possibly reflects that the low glucose could be a marker of cachectic/undernourished state

leading to or associated with TB. An undernourished state is known to be an important risk factor for TB.[17]

There are limitations to our study. First, HbA1C, possibly a better marker of glucose control, was not available in our cohort. Also, information about use of anti-diabetic medications or formally validated information about diabetes diagnosis was not available. However, it could be argued that higher risk of TB in diabetics is largely mediated by higher blood glucose, which was measured in our study. Second, non-availability of blood glucose in all participants could possibly lead to selection bias. Also, in this younger population, there were only a few participants in the extreme categories of the glucose, possibly leading to loss of power in some of the models. Glucose was not measured in a standardised fashion and it is possible that for some patients it may not be a post-fasting level. Finally, important variables such as smoking, diet details, and isoniazid prophylaxis were not available. These limitations would likely cause bias toward the null and would underestimate relationships. Our findings nevertheless need to be verified in larger studies.

Blood glucose control could play an important role in modifying the risk of TB in treated HIV-positive individuals. Indeed, studies in general population from China and India have suggested that more vigilant screening for TB in diabetics could be a worthwhile approach.[18-20] Future studies should investigate whether such an approach (and possibly enhanced screening for DM in TB patients[7, 19]) in treated HIV-positive individuals further improves clinical outcomes.

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Table-1

Unadjusted and adjusted analyses for the relationship between glycemia and the TB outcome

Variables	Events (n)/person-years (×100)/Rate per 100 person-years Total: 303/192.34/1.58	Univariate (unadjusted) models stratified by site HR (95% CI), P-value	Adjusted models further stratified by site*** HR (95% CI), P-value
Baseline (study entry) glucose deciles (cut-off mmol/L)			
1(≤4.10)	31/15.98/1.94	1.43 (0.81 to 2.55)	1.29 (0.72 to 2.32)
2(4.40)	48/17.68/2.71	2.19 (1.30 to 3.71)	2.16 (1.27 to 3.66)
3(4.60)	20/18.20/1.10	0.99 (0.53 to 1.85)	0.98 (0.53 to 1.84)
4(4.79)	31/21.09/1.47	1.48 (0.84 to 2.61)	1.51 (0.86 to 2.67)
5(4.96)	33/20.55/1.61	1.70 (0.97 to 2.96)	1.71 (0.98 to 3.00)
6(5.15)	20/19.71/1.01	Reference	Reference
7(5.39)	34/21.11/1.61	1.59 (0.91 to 2.76)	1.58 (0.91 to 2.76)
8(5.70)	18/20.03/0.89	0.93 (0.49 to 1.76)	0.93 (0.49 to 1.76)
9(6.55)	29/20.08/1.44	1.34 (0.75 to 2.37)	1.33 (0.75 to 2.36)
10(>6.55)	39/17.91/ 2.18	1.95 (1.13 to 3.36)	1.71 (1.01 to 2.96)
Overall P*		0.009	0.020
Latest (time-updated) glucose deciles (cut-off mmol/L)			
1(≤4.18)	31/14.71/2.11	1.32 (0.73 to 2.40)	1.31 (0.72 to 2.40)
2(4.50)	54/21.10/2.56	2.05 (1.20 to 3.52)	2.21 (1.28 to 3.82)
3(4.68)	22/16.02/1.37	1.35 (0.72 to 2.53)	1.39 (0.74 to 2.62)
4(4.84)	34/20.01/1.70	1.57 (0.88 to 2.80)	1.84 (1.03 to 3.29)
5(5.01)	26/21.82/1.19	1.37 (0.75 to 2.51)	1.47 (0.80 to 2.71)
6(5.20)	18/20.97/0.86*	Reference	Reference
7(5.40)	26/18.80/1.38	1.46 (0.80 to 2.67)	1.63 (0.88 to 3.01)
8(5.78)	27/20.44/1.32	1.49 (0.81 to 2.71)	1.57 (0.85 to 2.89)
9(6.55)	27/20.75/1.30	1.42 (0.78 to 2.59)	1.50 (0.82 to 2.76)
10(>6.55)	38/17.69/2.15	1.97 (1.12 to 3.47)	1.91 (1.07 to 3.41)
Overall P**		0.163	0.126

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Variables	Events (n)/person-years (×100)/Rate per 100 person-years Total: 303/192.34/1.58	Univariate (unadjusted) models stratified by site HR (95% CI), P-value	Adjusted models further stratified by site*** HR (95% CI), P-value
Diabetic range (≥7mmol/L) ever			
No	228/150.12	Reference	Reference
Yes	75/42.22	1.45 (1.10 to 1.92)	1.34 (1.01 to 1.79)
P-value		0.009	0.049

* Chosen as reference category due to lowest event rate (in latest glucose analysis).

** Overall P-value for heterogeneity calculated by likelihood ratio test.

*** Models adjusted for age, gender, body mass index, CD4 count, report of injecting drug use, use of antiretroviral therapy (see Methods section for details). In the final models, all of these variables were significantly associated with the outcome (data not shown).

NOTE: TB=tuberculosis.